DETAILED ACTION

1. This office action is in response to an amendment filed April 21, 2009. Claims 1-48 were previously pending, with claims 29-39 withdrawn from consideration. Applicants amended claims 1, 8, 22, 25, 40 and 46 and cancelled claims 2, 3, 23 and 24. Claims 1, 4-22, and 25-48 are pending, claims 29-39 are withdrawn from consideration.

2. Applicants are notified that the instant amendment is not in compliance with the rule under 37 C.F.R. 1.121, since the full text of the withdrawn claims is not provided. However, in order to advance prosecution the amendment is being considered. In a subsequent reply Applicants are required to provide an amendment that complies with the rules.

3. Applicants' amendments overcame all of the previously presented rejections. Amendments to claims 1, 25 and 40 overcame all of the previously presented rejections for these claims by incorporating SEQ ID NO: 11, for which no art was found teaching or suggesting the sequence. Therefore claims 1, 4-21, 25-28 and 40-45 are allowed.

4. With respect to claims 22 and 46-48, claim 22 was amended to incorporate limitations of claims 23 and 24, which were previously rejected, therefore claim 22 will be rejected over the same references as claims 23 and 24. Claim 46 was amended to recite primers with SEQ ID NO: 1 and 2, therefore new grounds for rejection will be provided for claims 46-48. Applicants' arguments regarding the previously presented rejections are addressed in the "Response to Arguments" section below.

5. Applicants' amendment to the specification obviated the objection presented in the previous office action.

6. Applicants' submission of the text file of the sequence listing is sufficient to satisfy the sequence submission rules.

Response to Arguments

7. Applicant's arguments filed April 21, 2009 have been fully considered but they are not persuasive.

A) Regarding the rejection of claim 2 under 35 U.S.C. 103(a) over Van der Zee et al. and Wittwer et al. (U.S. Patent No. 6,174,670), in view of Mc Lafferty et al. and Buck et al. and the rejection of claims 23 and 24 under 35 U.S.C. 103 (a) over Van der Zee et al. (=Van der Zee1) and Wittwer et al. (U.S. Patent No. 6,174,670), in view of Van der Zee et al. (=Van der Zee2) and Buck et al., Applicants argue the following:

A) Buck et al. teaches an automated sequencing reaction which is significantly different than a PCR amplification reaction, which uses at least two oligonucleotides, or a real-time PCR, in which four oligonucleotides are used, therefore primer design for real-time amplification is not always predictable. In support of this argument Applicants submitted the references of Elnifro et al., Tichopad et al., Abd-Elsalam, all of which deal with primer design in general, a reference of Csordas et al., which deals with selection of primers for detection of Salmonella enterica by real-time PCR.

B) In view of KSR v. Teleflex, the "known options" in the art are not "finite, identified and predictable".

C) In re Deuel is not relevant to the instant claims since the case dealt with the obviousness of nucleic acid sequences over references which disclosed an amino acid sequence, therefore In re Deuel does not indicate that a primer or probe sequence complementary to the target is a structural homolog.

D) Claimed primers and probes are not obvious over the cited references as supported by In re Bell.

E) The primer and probe sequences of SEQ ID NO: 1, 2, 5, 6, 12 and 13 are not obvious because their combination leads to high sensitivity and specificity towards their targets, as shown in Examples 10 and 11. Applicants further argue that each of the probes (SEQ ID NO: 3, 12 and 13) has a particular melting temperature which can be used to confirm the presence of Bordetella in the sample.

Regarding A), sequencing, PCR amplification and real-time PCR are the same process which may differ in the number of primers involved. All three processes require the same fundamental steps: design and synthesis of primers, annealing of primers to a selected sequence and extension of the 3' ends of the primers by a polymerase. Applicants argues that sequencing uses only one primer, however, this is not true, since usually both DNA strands are sequenced to avoid errors. Further, for very long sequences of more than 1000 bp, more than one sequencing primer is used. Therefore, both sequencing and PCR require at least two primers, one for each strand of the DNA. Further, even though real-time PCR may require three or four oligonucleotides (one or two of them serving as a probe), only two of them are primers, while the other serve as probes binding to the amplified fragments. Therefore, sequencing, PCR amplification and real-time PCR use two primers in a process governed by the same principles. In conclusion, selection of primers for sequencing is not qualitatively different from the selection of primers for PCR amplification or real-time PCR. Finally, Buck et al. provides evidence that 95 18 bp primers selected from a sequence of 300 bp at 3 bp intervals all perform as specific primers, and thus Buck et al. provides EVIDENCE of the equivalence of primers in extension type assays, which include PCR. Applicants's arguments cannot rebut this evidentiary showing.

The references provided by Applicants do not provide evidence that Applicants's primer selection was in any way unique. The references of Elnifro et al., Tichopad et al. and Abd-Elsalam

all deal with primer design in general, and contain information well known to one of skill in the art how to select primers. The reference of Csordas et al., which deals with selection of primers for detection of Salmonella enterica by real-time PCR, is pertinent to this case in that even though previously known primer sets were found by Csordas et al. to be somewhat deficient when used in real-time PCR, a primer set designed using automated software based on the known gene sequence performed as expected, with high sensitivity and specificity (see page 189, fourth paragraph; page 191, paragraphs 5-9). Therefore, Csordas et al. actually provide evidence that primer selection using automated software results in selection of sensitive and specific primers, further supporting the expectation of success of designing primers based on a known sequence using software programs, as routinely used in the art.

Applicants's own evidence in form of Example 2, first paragraph, does not show that any specific region of the known IS481 and IS1001 sequences were targeted by Applicants for amplification based on any special properties of these regions. There is no evidence in Applicants's disclosure that any of the primers selected were additionally tested before being used in the amplification reactions. Applicants did not provide any evidence that primers and/or probes selected from any other regions of these sequences fail to amplify them.

Regarding B), the genus of nucleic acids represented by fragments of a given nucleic acid sequence is not very large. For example, the IS481 sequence (GenBank Accession No. M22031) is 1053 bp long. The number of 20 bp oligonucleotides derived from that sequence every base pair would be 1053-20 +1 =1034 oligonucleotides, which is not a huge genus. The IS1001 sequence (GenBank Accession No. X66858) is 1306 bp long. The number of 20 bp oligonucleotides derived from that sequence every base pair would be 1306-20 +1 =1287 oligonucleotides, which is not a huge genus as well. Using a primer design software would allow elimination of structurally

unwanted primers, making the number much smaller. Further, even if several pairs of primers were to be tested to determine whether they worked in a particular amplification reaction, this is a routine experimentation process, not an inventive one.

Regarding C), it is not relevant what In re Deuel was about, since the Court's statement provided in the rejection refers to any structurally similar compounds. The fact that In re Duel does not specifically discuss primers or probes and target nucleic acids does not diminish the relevance of that statement. In fact, one would be hard pressed to find better examples of structural homologs than primers and probes, which are parts of the same target nucleic acid molecule by virtue of being complementary to one of the strands of the molecule.

Regarding D), the case of In re Bell the issue was whether the presence of an amino acid sequence of a protein in prior art combined with knowledge of how to isolate genes would render the claimed nucleic acids obvious. Therefore, since translating an amino acid sequence into a nucleic acid results in many possible nucleic acids because of the codon degeneracy, the Court concluded that the nucleic acids would not have been obvious. However, the issue in the instant case is whether two different nucleic acid fragments selected from the same nucleic acid sequence would be equivalent in their function as primers, therefore In re Bell is irrelevant to the instant claims.

Regarding E) The IS481 sequence is specific for B. pertussis, and the IS1001 sequence is specific for B. parapertussis, and primers used by Van der Zee et al. detected both with high specificity and sensitivity (Fig. 3; Fig. 4; page 2138, fourth paragraph). Further, even if the primers and probes were not sensitive and/or specific, given a sequence from which to pick them and a ubiquity of sequence alignment and primer design tools, finding a primer pair which is specific and/or sensitive amounts to following directions and performing routine optimization, which are not

inventive processes. Finally, the particular melting temperatures of the probes are not limitations in the claims, and every primer or probe has a melting temperature which is dependent on the solution composition and the primer or probe sequence, therefore a melting temperature is an inherent property of any primer or probe.

The rejections are restated to account for claim amendments.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (=Van der Zee1) (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993; cited in the previous office action), Wittwer et al. (U.S. Patent No. 6,174,670; cited in the previous office action), Van der Zee et al. (=Van der Zee2) (J. Bacteriol., vol. 175, pp. 141-147, 1993; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action).

A) Regarding claim 22, Van der Zee et al. teach a method for detecting the presence or absence of Bordetella parapertussis in a biological sample from an individual, said method comprising:

performing at least one cycling step, wherein a cycling step comprises an amplifying step and a hybridizing step, wherein said amplifying step comprises contacting said sample with a pair of IS1001 primers to produce an IS1001 amplification product if a B. parapertussis IS1001 nucleic acid molecule is present in said sample, wherein said hybridizing step comprises contacting said sample with a pair of IS1001 probes, wherein the members of said pair of IS1001 probes hybridize

within no more than five nucleotides of each other, wherein a first IS1001 probe of said pair of IS1001 probes is labeled with a donor fluorescent moiety and a second IS1001 probe of said pair of IS1001 probes is labeled with a corresponding acceptor fluorescent moiety (Van der Zee et al. teach amplification of B. parapertussis in samples from patients to detect the presence or absence of B. parapertussis (Abstract). The samples were amplified with a pair of IS1001-specific primers by PCR (page 2135, second paragraph; page 2136, second paragraph). Amplification products are detected with a digoxigenin-labeled probe specific for IS1001 sequences (page 2136, fourth and fifth paragraphs).); and

detecting the presence or absence of fluorescence resonance energy transfer (FRET) between said donor fluorescent moiety of said first IS1001 probe and said corresponding acceptor fluorescent moiety of said second IS1001 probe (Van der Zee et al. teach detection of the amplification products with ethidium bromide (Fig. 3, 4) and teach detection of amplification products with the probes (Fig. 5).).

B) Van der Zee et al. do not teach detection of amplification products with a probe consisting of two segments, one of which is labeled with donor and the other with acceptor.

C) Wittwer et al. teach real-time detection of amplification products.

Regarding claim 22, Wittwer et al. teach detection of amplification products in real time by using two probes, one labeled with a fluorescent donor, the other with a fluorescent acceptor (col. 5, lines 21-41; Fig. 5C). The probe detection utilizes the fluorescence resonance energy transfer (FRET) (col. 19, lines 40-63). The fluorescence is monitored for both of the fluorophores (col. 21, lines 58-65). The probes were used to monitor amplification of different starting amounts of beta-globin. The presence of FRET between the two fluorophores was indicative of the presence of

nucleic acid template in the sample (col. 30, lines 30-60, col. 31, lines 22-28; Fig. 17). The optimum spacing of the probes is from zero to 5 bases (col. 28, lines 8-26).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used FRET-based amplification detection techniques of Wittwer et al. in the B. pertussis and B. parapertussis detection method of Van der Zee et al. The motivation to do so, provided by Wittwer et al., would have been that PCR was performed rapidly and the reaction monitored continuously, allowing adjustment of parameters (col. 4, lines 15-18), the total time required for PCR amplification and analysis was decreased (col. 4, lines 27-31) and desired from undesired products and different amplification products were distinguished on the basis of melting curves (col. 5, lines 1-15).

D) Van der Zee1 teach IS1001-specific primers BPPA and BPPZ, hybridizing to bp 1211-1232 and 734-755 of IS1001, and a probe cut out from the IS1001 with PstI (page 2136, second and fourth paragraphs). Van der Zee1 teach that the primers based on a IS1001 sequence of Van der Zee2 (page 2136, second paragraph). The GenBank accession number for that sequence is X66858. Van der Zee1 do not specifically teach primers with SEQ ID NO: 5 and 6 and probes with SEQ ID NO: 12 and 13.

E) As can be seen from sequence alignments, SEQ ID NO: 5 is complementary to bp 375-392 of the IS1001 sequence of Van der Zee2, SEQ ID NO: 6 is complementary to bp 556-574 of the IS1001 sequence of Van der Zee2, SEQ ID NO: 12 is complementary to bp 470-488 of the IS1001 sequence of Van der Zee2, and SEQ ID NO: 13 is complementary to bp 490-504 of the IS1001 sequence of Van der Zee2 et al.

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X66858
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DEFINITION  B.parapertussis insertion sequence IS1001 TnpA gene for
            transposase.
ACCESSION   X66858 S51601
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VERSION     X66858.1  GI:39755
KEYWORDS    insertion sequence; insertion sequence IS1001; tnpA gene;
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SOURCE      Bordetella parapertussis
  ORGANISM  Bordetella parapertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
            Alcaligenaceae; Bordetella.
REFERENCE   1
  AUTHORS   van der Zee,A., Agterberg,C., van Agterveld,M., Peeters,M. and
            Mooi,F.R.
  TITLE     Characterization of IS1001, an insertion sequence element of
            Bordetella parapertussis
  JOURNAL   J. Bacteriol. 175 (1), 141-147 (1993)
   PUBMED   8093238
REFERENCE   2  (bases 1 to 1306)
  AUTHORS   van der Zee,A.
  TITLE     Direct Submission
  JOURNAL   Submitted (12-JUN-1992) A. Van Der Zee, National Insitute of Health
            &, Environmental Protection, A Van Leeuwenhoeklaan 9, P O Box 1,
            3720 BA Bilthoven, THE NETHERLANDS
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X66858/c
LOCUS       X66858                  1306 bp    DNA     linear   BCT 07-JUL-2002
DEFINITION  B.parapertussis insertion sequence IS1001 TnpA gene for
            transposase.
ACCESSION   X66858 S51601
VERSION     X66858.1  GI:39755
KEYWORDS    insertion sequence; insertion sequence IS1001; tnpA gene;
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SOURCE      Bordetella parapertussis
  ORGANISM  Bordetella parapertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
            Alcaligenaceae; Bordetella.
REFERENCE   1
  AUTHORS   van der Zee,A., Agterberg,C., van Agterveld,M., Peeters,M. and
            Mooi,F.R.
  TITLE     Characterization of IS1001, an insertion sequence element of
            Bordetella parapertussis
  JOURNAL   J. Bacteriol. 175 (1), 141-147 (1993)
   PUBMED   8093238
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  JOURNAL   Submitted (12-JUN-1992) A. Van Der Zee, National Insitute of Health
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            3720 BA Bilthoven, THE NETHERLANDS
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ACCESSION   X66858 S51601
VERSION     X66858.1  GI:39755
KEYWORDS    insertion sequence; insertion sequence IS1001; tnpA gene;
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SOURCE      Bordetella parapertussis
  ORGANISM  Bordetella parapertussis
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            Alcaligenaceae; Bordetella.
REFERENCE   1
  AUTHORS   van der Zee,A., Agterberg,C., van Agterveld,M., Peeters,M. and
            Mooi,F.R.
  TITLE     Characterization of IS1001, an insertion sequence element of
            Bordetella parapertussis
  JOURNAL   J. Bacteriol. 175 (1), 141-147 (1993)
   PUBMED   8093238
REFERENCE   2  (bases 1 to 1306)
  AUTHORS   van der Zee,A.
  TITLE     Direct Submission
  JOURNAL   Submitted (12-JUN-1992) A. Van Der Zee, National Insitute of Health
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X66858
LOCUS       X66858                  1306 bp    DNA     linear   BCT 07-JUL-2002
DEFINITION  B.parapertussis insertion sequence IS1001 TnpA gene for
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ACCESSION   X66858 S51601
VERSION     X66858.1  GI:39755
KEYWORDS    insertion sequence; insertion sequence IS1001; tnpA gene;
            transposase.
SOURCE      Bordetella parapertussis
  ORGANISM  Bordetella parapertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
            Alcaligenaceae; Bordetella.
REFERENCE   1
  AUTHORS   van der Zee,A., Agterberg,C., van Agterveld,M., Peeters,M. and
            Mooi,F.R.
  TITLE     Characterization of IS1001, an insertion sequence element of
            Bordetella parapertussis
  JOURNAL   J. Bacteriol. 175 (1), 141-147 (1993)
   PUBMED   8093238
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  TITLE     Direct Submission
  JOURNAL   Submitted (12-JUN-1992) A. Van Der Zee, National Insitute of Health
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Db        490 GCTGGACAAGGCTCG 504
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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Van der Zee1 and Wittwer et al. with the use of functionally equivalent primers selected from the sequence of Van der Zee1, since Van der Zee1 expressly teach primer selection for amplification of B. parapertussis from published sequence and since Van der Zee2 provide such published sequence.

In the decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural

relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. parapertussis, and concerning that a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

10. Claims 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993; cited in the previous office action), Mc Lafferty et al. (J. Gen. Microbiol., vol. 134, pp. 2297-2306, 1988; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action).

A) Regarding claim 46, Van der Zee et al. teach a method for detecting the presence or absence of B. pertussis in a biological sample from an individual, said method comprising:

performing at least one cycling step, wherein a cycling step comprises an amplifying step and a dye-binding step, wherein said amplifying step comprises contacting said sample with a pair of IS481 primers to produce an IS481 amplification product if a B. pertussis IS481 nucleic acid molecule is present in said sample, wherein said dye-binding step comprises contacting said IS481 amplification product with a nucleic acid binding dye (Van der Zee et al. teach amplification of B. pertussis in samples from patients to detect the presence or absence of B. pertussis (Abstract). The samples were amplified with a pair of IS481-specific primers by PCR (page 2135, second paragraph; page 2136, second paragraph). The amplification products were contacted with ethidium bromide (= dye) by electrophoresing them on a gel containing the dye (page 2136, fifth paragraph).); and

detecting the presence or absence of binding of said nucleic acid binding dye to said amplification product (Van der Zee et al. teach detection of the amplification products (Fig. 3 and 4).),

wherein the presence of binding is indicative of the presence of B. pertussis in said sample, and wherein the absence of binding is indicative of the absence of B. pertussis in said sample (Van

der Zee et al. teach that the presence of a 288 bp amplification product indicates presence of B. pertussis in the sample; Fig. 3, 4; Table 3; page 2138, last paragraph; page 2139, first paragraph).).

Regarding claim 47, Van der Zee et al. teach ethidium bromide (page 2136, fifth paragraph).

Regarding claim 46, Van der Zee et al. teach IS481-specific primers BP1 and BP4, hybridizing to bp 208-228 and 476-496 of IS481. Van der Zee et al. teach the primers based on an IS481 sequence of McLafferty et al. (page 2136, second paragraph). The sequence of McLafferty et al. is presented in the GenBank Accession No. M22031.

B) Van der Zee et al. do not specifically teach primers with SEQ ID NO: 1 and 2.

C) As can be seen from sequence alignments, SEQ ID NO: 1 is complementary to bp 684-701 of the IS481 sequence of McLafferty et al., SEQ ID NO: 2 is complementary to bp 895-917 of the IS481 sequence of McLafferty et al.

```
BPETERRA
LOCUS       BPETERRA                1053 bp    DNA     linear   BCT 26-APR-1993
DEFINITION  B.pertussis insertion sequence with 28 bp terminal inverted repeats
            DNA.
ACCESSION   M22031
VERSION     M22031.1  GI:144060
KEYWORDS    insertion sequence.
SOURCE      Bordetella pertussis
  ORGANISM  Bordetella pertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
            Alcaligenaceae; Bordetella.
REFERENCE   1  (bases 1 to 1053)
  AUTHORS   McLafferty,M.A., Harcus,D.R. and Hewlett,E.L.
  TITLE     Nucleotide sequence and characterization of a repetitive DNA
            element from the genome of Bordetella pertussis with
            characteristics of an insertion sequence
  JOURNAL   J. Gen. Microbiol. 134 (Pt 8), 2297-2306 (1988)
   PUBMED   2908119
COMMENT     Original source text: B.pertussis DNA.
FEATURES             Location/Qualifiers
     source          1. .1053
                     /organism="Bordetella pertussis"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:520"
     repeat_region   1. .28
                     /note="inverted repeat"
     repeat_region   1026. .1053
                     /note="inverted repeat"
ORIGIN
```

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  Query Match             100.0%;  Score 18;  DB 14;  Length 1053;
  Best Local Similarity   100.0%;  Pred. No. 91;
  Matches   18;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CCAGTTCCTCAAGGACGC 18
              ||||||||||||||||||
Db        684 CCAGTTCCTCAAGGACGC 701

BPETERRA/c
LOCUS       BPETERRA                1053 bp    DNA     linear   BCT 26-APR-1993
DEFINITION  B.pertussis insertion sequence with 28 bp terminal inverted repeats
            DNA.
ACCESSION   M22031
VERSION     M22031.1  GI:144060
KEYWORDS    insertion sequence.
SOURCE      Bordetella pertussis
  ORGANISM  Bordetella pertussis
            Bacteria; Proteobacteria; Betaproteobacteria; Burkholderiales;
            Alcaligenaceae; Bordetella.
REFERENCE   1  (bases 1 to 1053)
  AUTHORS   McLafferty,M.A., Harcus,D.R. and Hewlett,E.L.
  TITLE     Nucleotide sequence and characterization of a repetitive DNA
            element from the genome of Bordetella pertussis with
            characteristics of an insertion sequence
  JOURNAL   J. Gen. Microbiol. 134 (Pt 8), 2297-2306 (1988)
   PUBMED   2908119
COMMENT     Original source text: B.pertussis DNA.
FEATURES             Location/Qualifiers
     source          1. .1053
                     /organism="Bordetella pertussis"
                     /mol_type="genomic DNA"
                     /db_xref="taxon:520"
     repeat_region   1. .28
                     /note="inverted repeat"
     repeat_region   1026. .1053
                     /note="inverted repeat"
ORIGIN

  Query Match             100.0%;  Score 23;  DB 14;  Length 1053;
  Best Local Similarity   100.0%;  Pred. No. 0.41;
  Matches   23;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GAGTTCTGGTAGGTGTGAGCGTA 23
              |||||||||||||||||||||||
Db        917 GAGTTCTGGTAGGTGTGAGCGTA 895
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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Van der Zee et al. with the use of functionally equivalent primers selected from the sequence of McLafferty et al., since Van der Zee et al.

expressly teach primer selection from the B. pertussis published sequence and since McLafferty et al. provide such published sequence.

In the decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. pertussis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as

well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

11. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Zee et al. (J. Clin. Microbiol., vol. 31, pp. 2134-2140, 1993; cited in the previous office action), Mc Lafferty et al. (J. Gen. Microbiol., vol. 134, pp. 2297-2306, 1988; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action), as applied to claims 46 and 47 above, and further in view of Wittwer et al. (U.S. Patent No. 6,174,670).

A) Van der Zee et al. teach detection of amplification products using ethidium bromide, but do not teach determination of the melting temperature between the amplification product and the nucleic acid binding dye.

B) Regarding claim 48, Wittwer et al. teach determination of the melting curves of three different amplification products using SYBRGreenI. The three fragments were amplified from hepatitis B surface antigen, PSA and beta-globin genes. They could be distinguished on the basis of the differences in their melting temperatures (col. 37, lines 49-67; col. 38, lines 1-27; Fig. 37).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used temperature melting profiles of Wittwer et al. in the method of Van der Zee et al., McLafferty et al. and Buck et al. The motivation to do so was expressly provided by Wittwer et al. (col. 4, lines 64-67; col. 5, lines 1-11):

"In accordance with another aspect of the present invention, fluorescence monitoring is used to acquire product melting curves during PCR by fluorescence monitoring with double-strand-specific DNA specific dyes. Plotting fluorescence as a function of temperature as the thermal cycler heats through the dissociation temperature of the product gives a PCR product melting curve. The shape and position of this DNA melting curve is a function of GC/AT ratio, length, and sequence, and can be used to differentiate amplification products separated by less than 2° C in melting temperature. Desired products can be distinguished from undesired products, including primer dimers. Analysis of melting curves can be used to extend the dynamic range of quantitative PCR and to differentiate different products in multiplex amplification."

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
July 16, 2009